***Remarks:***

*Claims*

The number of total claims and of independent claims remains less than the amount for which fees were previously paid. Notwithstanding, Applicants hereby authorize the Commissioner to charge any additional claim fees required by entry of this Amendment to Deposit Account No. 50-0258.

By the present amendment claims 55-59, 61, 64 and 66-68 have been amended to more particularly and distinctly define the subject matter of the invention. New claim 69 has been added. Claims 55-59, 61, and 63-69 are pending. Support for this amendment is either apparent, or is as described in the text below. Support for the recitation of recombinant polypeptide can be found at, for example, page 1, lines 5-9; page 3, lines 14-15; page 6, lines 21-24; page 7, lines 13-19; and page 8, lines 13-16. No new matter is added.

*Claim Rejections under 35 U.S.C. §102(a)*

Claims 55, 56 and 61 stand rejected under 35 U.S.C. §102(a) as being anticipated by Martin et al. In particular, the Examiner asserts that Martin et al. discloses outer membrane protein from whole cell lysate preparations from N. meningitidis. The Examiner notes that monoclonal antibodies were produced by immunizing mice with the OM preparation, indicating that the disclosed outer membrane protein was immunogenic. The Examiner alleges that the disclosed composition, i.e., whole cell lysates from N. meningitidis in buffer inherently comprise the amino acid sequence as set forth in SEQ ID NO:2.

Without conceding the correctness of the rejection, Applicant has amended claims 55, 56 and 61 to more particularly distinctly claim the subject matter of his invention. It is submitted that the amended claims recite an isolated, recombinant polypeptide. The claimed isolate is not disclosed or suggested by the OMP preparations described in Martin et al. Reconsideration and withdrawal of the rejection is respectfully requested.

*Claim Rejections under 35 U.S.C. §112, First Paragraph - Written Description*

Claims 55-58, 61 and 63-68 stand rejected under 35 U.S.C. 112, first paragraph as containing subject matter which was not described in the specification in such a way as to

reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. In particular, the Examiner alleges that the specification does not teach immunogenic fragments (i.e., 15 or 20 amino acids) of an isolated polypeptide comprising SEQ ID NO:2, immunogenic compositions comprising the fragments, or fusion proteins comprising said fragments. In particular, the Examiner posits:

> The specification fails to teach an isolated polypeptide fragments of SEQ ID NO:2 and it is noted that the claimed fragments do not exist as an invention independent of their function in encoding a protein, SEQ ID NO:2. The actual structure or other relevant identifying characteristics of each protein fragment having the claimed properties of the protein can only be determined empirically by actually making every nucleic acid that encodes the recited fragments and testing each to determine whether such fragment having the particularly disclosed properties of the full length protein. For example, if there is a well-established correlation between structure and function in the art, one skilled in the art will be able to reasonable predict the complete structure of the claimed invention from its function. This specification does not teach such, and the art is devoid of this correlation for SEQ ID NO:2 protein with undetermined function. There is no written description for an isolated fragments comprising 15 amino acids or 20 amino acids or immunogenic composition or fusion protein comprising said fragments as claimed.
>
> The isolated polypeptide comprising of SEQ ID NO:2 is uncharacterized by this specification and is not asserted to belong to any known family of proteins. The specification fails to teach the structure or relevant identifying characteristics of a representative number of SEQ ID NO:2 fragments, sufficient to allow one skilled in the art to determine that the inventor had possession of the invention as claimed. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc V Chuaai Pharmaceutical Co Ltd., 18 USPQ2d 1016. One cannot describe what one has not conceived. See Fiddes v. Baird, 30 USPQ2d 1481, 1483. In Fiddes v. Baird, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class.

Applicant respectfully disagrees. As noted in the Notice, entitled, "*Guidelines for*

*Examination of Patent Applications under the 35 U.S.C. 112, ¶1. Written Description" Requirement* at p. 1104, vol 66, no. 4 (January 5, 2001) (emphasis added):

> An applicant shows possession of the claimed invention with all its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. Possession may be shown in a variety of ways including description of an actual reduction to practice, or by showing that the invention was "ready for patenting" by the disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing characteristics sufficient to show that the applicant was in possession of the claimed invention.

Applicant notes that the specification discloses the description of an immunogenic fragment of a BASB040 polypeptide, that is a contiguous portion of the BASB040 polypeptide which has the same or substantially the same immunogenic activity as the polypeptide comprising the amino acid sequence of SEQ ID NO:2, at, for example, page 5, lines 4-7. In addition, the specification further describes preferred fragments including an isolated polypeptide comprising amino acid sequence having at least 15 (or 20) contiguous amino acids of SEQ ID NO:2 at, for example, page 6, lines 5-7. Applicant submits that these recitations of the immunogenic fragments, coupled with the disclosed amino acid sequence of SEQ ID NO:2 represents possession of the invention by showing that the invention was "ready for patenting" by the disclosure of structural chemical formulas that show the invention was complete.

Moreover, Applicant respectfully disagrees with the contention that the specification is silent with respect to fusion proteins comprising said immunogenic fragments or immunogenic compositions comprising said fragments. With respect to fusion proteins, the specification, for example, discloses the following at page 6, line 19 through page 7, line 5 (emphasis added):

> The polypeptides, or immunogenic fragments, of the invention may be in the form of the "mature" protein or may be a part of a larger protein such as a precursor or a fusion protein. It is often advantageous to include an additional amino acid sequence which contains secretory or leader sequences, pro-sequences, sequences which aid in purification such as multiple histidine residues, or an additional sequence for stability during recombinant production. Furthermore, addition of exogenous polypeptide or lipid tail or

> polynucleotide sequences to increase the immunogenic potential of the final molecule is also considered.
>
> In one aspect, the invention relates to genetically engineered soluble fusion proteins comprising a polypeptide of the present invention, or a fragment thereof, and various portions of the constant regions of heavy or light chains of immunoglobulins of various subclasses (IgG, IgM, IgA, IgE). Preferred as an immunoglobulin is the constant part of the heavy chain of human IgG, particularly IgG1, where fusion takes place at the hinge region. In a particular embodiment, the Fc part can be removed simply by incorporation of a cleavage sequence which can be cleaved with blood clotting factor Xa.

With respect to immunogenic compositions, it is noted that vaccines (which are a type of immunogenic composition) containing fragments of BASB040 polypeptide are described at, for example, page 31, line 18 through page 32, line 6.

Accordingly, reconsideration of the Written Description Requirement rejection under 35 U.S.C. 112, ¶1 is respectfully requested.

*Claim Rejections - 35 U.S.C. §112, First Paragraph - Enablement*

Claims 55-58, 61 and 63-68 stand rejected under 35 U.S.C. §112, first paragraph, based on an assertion that the specification, while being enabling for a polypeptide consisting of SEQ ID NO:2, or immunogenic composition comprising the isolated polypeptide of SEQ ID NO:2 and a pharmaceutically acceptable carrier and an adjuvant; does not reasonably provide enablement for any isolated polypeptides comprising an immunogenic fragment of SEQ ID NO:2, wherein said immunogenic fragment comprises at least 15 or 20 amino acids. In addition, the Examiner contends that the specification does not enable fusion proteins comprising the polypeptide or fragments thereof, and a polypeptide selected to: provide T-helper epitopes, facilitate purification from a recombinant expression or stabilize the isolated polypeptide during recombinant expression.

The Examiner contends that the claims are not enabled because the written description is limited to only SEQ ID NO:2 which is encoded by BAS040 gene from N. meningitidis, ATCC 13090. The Examiner argues that the specification fails to teach that the claimed antigenic fragments are detected by immune sera, and lacks any description of such fragments.

Furthermore, the Examiner argues that the specification is silent in teaching fusion proteins as claimed.

The rejection also states that the specification fails to enable any fragments of SEQ ID NO:2 because: (1) the specification fails to teach fragments that are able to function by binding to immune sera; (2) the specification fails to make and use fragments that have an unknown or uncharacterized function; (3) the specification fails to teach what are the critical amino acid residues that can be modified and still achieve a fragment with functional activity; (4) due to evidence that replacement of a single amino acid residue in a protein leads to structural / functional changes in biological activity, there is reason to doubt the validity and functionality of the antigenic fragments of SEQ ID NO:2; and, (5) applicants have not displayed a nexus between the structure and function of the claimed fragments.

The rejection includes a general discussion of the unpredictability of protein chemistry, and on the consequences of a single change in an amino acid residue on the biological activity of a protein. The rejection concludes by asserting that the skilled artisan would be forced into undue experimentation to make and use the invention commensurate in scope with these claims.

Applicant respectfully disagrees. Whether the scope of enablement is sufficient is often decided in light of the following factors: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). These factors are illustrative, not mandatory. Amgen, Inc. v. Chugai Pharm. Co., Ltd., 927 F.2d 1200, 1213, 18 USPQ2d 1016, 1027 (Fed. Cir. 1991). A review of these factors as applied to the present claims, supports Applicant's assertion that the claims are enabled, as outlined in subsections (A) through (G) below.

**(A)** *Quantity Of Experimentation*

In Reece (Reece et al., 151 J. IMMUNOL. 6175 (1993), attached as Exhibit A)[1], in excess of one thousand (1,304) overlapping 12 residue peptide fragments were synthesized by the multipin method to map T-cell epitopes of tetanus toxin. Pools of 20 peptides each were used to simplify the mapping assays. Thus, it was practical to synthesize a large number of peptides, and the initial screen needed only to assay sixty to seventy pools. Pools that generated strong responses were deconvoluted by assaying the members of the pool. That such experimentation using a multipin method to screen for antigens is ordinary in this art is illustrated in CURRENT PROTOCOLS IN IMMUNOLOGY 9.7.1 (1997) (attached as Exhibit B) and Reece et al., 172 J. IMMUNOL. 241 (1994) (attached as Exhibit C). That such sequence-scanning techniques are ordinary in the art with respect to antibody-mediated antigenicity (as opposed to cellular immunity as in Reece) is illustrated in Geysen et al., 81 PROC. NATL. ACAD. SCI. USA 3998 (1984) (attached as Exhibit D).

Note that in Geysen, antisera to the whole antigen polypeptide was tested for specificity with an extensive scan of specific peptide sequences. This approach is quite useful to the present invention, where the full-length recombinant polypeptide that Applicant has isolated can readily be used within the state of the art to produce polyclonal antibodies. These polyclonal antibodies can then be used to screen for promising smaller polypeptide antigens.

**(B)** *Amount Of Direction Or Guidance Presented*

Guidance can be found in the specification at, for example, page 5, line 23 through page 6, line 3,

> Preferred fragments include, for example, truncation polypeptides having a portion of an amino acid sequence of SEQ ID NO:2,4,6 or of variants thereof, such as a continuous series of residues that includes an amino- and/or carboxyl-terminal amino acid sequence. Degradation forms of the polypeptides of the invention produced by or in a host cell, are also preferred. Further preferred are fragments characterized by structural or functional attributes such as fragments that comprise alpha-helix and alpha-helix forming

---

[1] The literature cited in this response provides evidence of the state of the art – and is not submitted under 37 CFR §1.56.

> regions, beta-sheet and beta-sheet forming regions, turn and turn-forming regions, coil and coil-forming regions, hydrophilic regions, hydrophobic regions, alpha amphipathic regions, beta amphipathic regions, flexible regions, surface-forming regions, substrate binding region, and high antigenic index regions.

That the sequence-based inferences described here are ordinary in the art, and of known value in selecting positive candidates is illustrated by CURRENT PROTOCOLS IN IMMUNOLOGY 9.3.1 (1991) (attached as Exhibit E).

**(C)** *Presence Or Absence Of Working Examples*

While the specification does not specifically provide a detailed working example for the isolation of immunogenic fragments of SEQ ID NO: 2, Applicant submits that a skilled artisan, given the teachings of the specification and recombinant techniques well known in the art, could readily prepare recombinant polypeptides comprising the claimed fragments of SEQ ID NO:2. Recombinant polypeptides comprising the fragments could then be used to produce protein-recognizing anti-sera using well-known immunological techniques. The anti-sera's potential for detecting the presence of SEQ ID NO:2 can then be determined. Moreover, the ease with which the polypeptides are screened, and the availability of robotic automation tools at the time the application was filed, counterbalance this element of the analysis.

**(D)** *Nature Of The Invention; Predictability Or Unpredictability Of The Art*

The art is no more unpredictable than the chemical arts in general. Thus, the reasonable scope of the claims should be comparable to that which can be achieved with other structure-focused claims in the chemical arts. Moreover, the ease with which the polypeptides are screened, and the availability of robotic automation tools at the time the application was filed, counterbalance this element of the analysis.

That an unpredictable art nonetheless allows for reasonable inferences of claim scope is illustrated by the following text from the case law:

> Appellants have apparently not disclosed *every* catalyst which will work; they have apparently not disclosed *every* catalyst which will not work. The question, then, is whether in an unpredictable art, section 112 requires disclosure of a test with *every* species covered

> by a claim. To require such a complete disclosure would apparently necessitate a patent application or applications with "thousands" of examples or the disclosure of "thousands" of catalysts along with information as to whether each exhibits catalytic behavior resulting in the production of hydroperoxides. More importantly, such a requirement would force an inventor seeking adequate patent protection to carry out a prohibitive number of actual experiments. This would tend to discourage inventors from filing patent applications in an unpredictable area since the patent claims would have to be limited to those embodiments which are expressly disclosed. A potential infringer could readily avoid "literal" infringement of such claims by merely finding another analogous catalyst complex which could be used in "forming hydroperoxides."

Application of Angstad, 537 F.2d 498, 502-3, 190 USPQ 214, 218 (CCPA1976) (emphasis in the original).

**(E)** *State Of The Prior Art*

The highly advanced state of this art is illustrated by the above cited 1984 article by Geysen. The other articles discussed above clearly show that sequence scanning for antigenicity is a highly developed art.

**(F)** *Relative Skill Of Those In The Art*

In Enzo Biochem, Inc. v. Calgene, Inc., 188 F.3d 1362, 52 USPQ2d 1129 (Fed. Cir. 1999), the Federal Circuit approved a trial court determination in a comparable art that a person of ordinary skill would be a junior faculty member with one or two years of relevant experience or a postdoctoral student with several years of experience. Applicants respectfully submit that this level of skill is an appropriate measure of skill in the present context.

**(G)** *Breadth Of The Claims*

The claims focus on a limited universe of claimed core elements. The world of the instant claims is miniscule compared to the monoclonal antibody world approved for claiming in In re Wands, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988).

The Wands factors thus weigh in favor of the allowability of the present claims. Reconsideration of this aspect of the rejection under 35 U.S.C. §112 is respectfully requested with respect to claims 55-58, 61 and 63-68.

*Claim Rejections under 35 U.S.C §103(a)*

As a preliminary matter, the Examiner contends that the application currently names joint inventors in her analysis of the patentability under 35 U.S.C. §103(a).

Applicant notes that the application documents including the "Declaration and Power of Attorney" and the "Filing Receipt" indicate only one inventor, namely, Jean-Louis Ruelle.

Claims 61 and 63-67 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Martin et al. (J. Ex. Med. Volume 185, No. 7, April 7, 1997, 1173-1184), and further in view of Prieels et al. (WO 94/00153). Martin et al. is as discussed above. The Examiner submits that Martin et al. does not disclose carrier, oil-in-water emulsion, aluminum salt and TH-1 type adjuvant 3D-MPL and QS21, but contends it would have been obvious to a person of ordinary skill in the art to combine the teachings of the two cited references.

Applicant submits that in view of the amendments to claims 55 and 61, the underpinnings of the rejection with respect to Martin et al. have been removed, thereby rendering the rejection under 35 U.S.C. §103(a) moot. Accordingly, reconsideration and withdrawal of the rejection is respectfully requested.